REVIEW ARTICLE

PATHOGENESIS, ETIOLOGY AND MANAGEMENT OF NASOPHARYNGEAL CARCINOMA

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ABSTRACT:
Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma (SCC) that usually develops around the ostium of the Eustachian tube in the lateral wall of the nasopharynx. The World Health Organization classifies NPC into three histopathological types based on the degree of differentiation. In endemic regions, NPC presents as a complex disease caused by an interaction of the oncogenic gamma herpes virus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process. The most common presenting symptom is cervical lymphadenopathy, followed by nasal, aural and neurological symptoms. Once the diagnosis is suspected on clinical grounds, histological confirmation of the diagnosis is mandatory. Radiotherapy is the mainstay treatment for early disease and concurrent cisplatin/radiotherapy has been demonstrated to prolong survival in locoregionally advanced disease. Ongoing studies of targeting agents and immunotherapeutic approaches may further improve treatment results.
Key words: Genetic, Histopathological, Nasopharyngeal carcinoma, Radiotherapy.

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INTRODUCTION

Cancer begins when cells in a part of the body start to grow out of control. There are manykinds of cancer, but they all start because of out-of-control growth of abnormal cells.Cancer cell growth is different from normal cell growth. Instead of dying, cancer cellscontinue to grow and form new, abnormal cells. Cancer cells can also invade other tissues, something that normal cells cannot do. In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulatethrough other tissues where they grow.Metastasis happens when thecancer cells get into the bloodstream or lymph vessels of our body.No matter where a cancer may spread, it is always named for the place where it started. Nasopharyngeal cancer is a cancer that starts in the nasopharynx, the upper part of the throatbehind the nose and near the base of skull. Nasopharyngeal carcinoma (NPC) is a squamous cellcarcinoma (SCC) that usually develops around the ostium of the Eustachian tube in the lateral wall of thenasopharynx[1]. This disease was initiallyreported in 1901 and characterized clinically in1922. NPC is a disease with a remarkablegeographic and racial distribution worldwide.

HISTOLOGICAL SUBTYPES OF NPC

The World Health Organization classifies NPC into three histopathological types based on the degree of differentiation. Type 1, SCC, is seen in5%–10% of cases of NPC and is characterized bywell-differentiated cells that produce keratin and demonstrated the presence of intracellular bridgeswhen observed under the electron microscope. Type2, nonkeratinizing squamous carcinoma, varies incell differentiation but does not produce keratin. Type 3 or undifferentiatedNPC constitutes the bulk of the tumors seen inpatients with NPC, is also nonkeratinizing, but is less differentiated, with highly variable cell types

[2].Types 2 and 3 NPC are Epstein–Barr virus (EBV) associated and have better prognoses than type 1;EBV infection is generally absent in type 1, especially in nonendemic areas. However, more recent data suggest that almost all NPC tumorsin the endemic areas, regardless of histologic subtype, have comorbid EBV infections, which is a strong evidencefor EBV as the etiology of NPC.[3] Undifferentiated NPC or type 3 was frequently characterized as lymphoepithelioma owing to the heavy infiltration of the primary tumor with lymphocytes.

ETIOLOGIES AND PATHOGENESIS

In endemic regions, NPC presents as a complex diseasecaused by an interaction of the oncogenic gamma herpes virus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process.

GENETIC FACTORS

While nasopharyngeal carcinoma is a rare malignancyin most parts of the world, it is one of the mostcommon cancers in Southeast Asia including areassuch as Southern China, Hong Kong, Singapore, Malaysia, and Taiwan. The familial risk of NPC is among the highest of any malignancy.[4] The described relative risk of NPC infirst-degree relatives is about 8.0.An important characteristic of familial cancers isthe early age onset of NPC.[5] Several linkage analyses studies suggested the association ofsusceptibility human leukocyte antigen (HLA) haplotypes with NPC development. The finding of translocation, amplification, and deletion of 3p, 5p, and 3qindicates that a minimal region of breakpoints is possiblefor contributing to NPC. Breakpoints have been frequentlyobserved in 1p11–31, 3p12–21, 3q25, 5q31, 11q13,12q13, and Xq25. Inactivation of tumorsuppressor genes on 3p, 9p, 11q, 13q, 14q, and 16q andalteration of oncogenes on chromosomes 8 and 12 are important in the development of NPC.Some studies suggested that genetic polymorphismsin genes that metabolize carcinogens areassociated with NPC susceptibility.

ENVIRONMENTAL FACTORS

A large number of case-control studies conducted indiverse populations (Cantonese, other SouthernChinese, Northern Chinese, and Thais) residing indifferent parts of Asia and North America have confirmed that Cantonese-style salted fish and otherpreserved foods containing large amounts of nitrosodimethyamine (NDMA), N-nitrospyrrolidene(NPYR), and N-nitrospiperidine (NPIP) may be carcinogenic factors for NPC.[6] Moreover, cigarette smoking and occupational exposure to formaldehyde andwood dust are recognized risk factors as well. Several studies conducted in high- and low-risk populations during the past decade have obviously implicated the nasopharynx as a tobacco susceptible cancer site [6].

EPSTEIN–BARR VIRUS

It was in 1966 when Old et al. first discovered the relationshipbetween EBV and NPC, using in situ hybridization and the anti-complement immune fluorescent assay.[7] Subsequent studies byothers demonstrated the expression of EBV latentgenes – Epstein–Barr virus nuclear antigen, latent membrane protein-1 (LMP-1), LMP-2, and EBVencoded small RNAs (EBER) – in NPC cells confirming the infection of tumor cells byEBV. Intriguingly, expression of EBV early antigen (EA) is positively correlated with the consumption of saltedand preserved food, suggesting that development ofEBV-positive NPC could be related to dietary habits, and provides another link to theepidemiological studies with NPC.

PRESENTATION, IMAGING AND STAGING

The most common presenting symptom is cervical lymphadenopathy, followed by nasal, aural and neurological symptoms.Only 5% of patients present with distant metastases in series from Southern China.[8,9] Once the diagnosis issuspected on clinical grounds, histological confirmation of thediagnosis is mandatory. The technique of biopsy under localanesthesia has been found to have a diagnostic sensitivitycomparable to that obtained by examination under generalanesthesia. The biopsy is facilitated by direct visualization of the nasopharynx with a fiberoptic nasopharyngoscope. However, since the biopsy may cause soft tissue swelling and/or ahematoma, computed tomography scan and magneticresonance imaging of the nasopharynx and the skull base should be undertaken before the biopsy.The primary tumor extent should be evaluated by both CT scan and MRI. The latter is more sensitive than CT scan for thedetection of the primary tumor, its direct soft tissue extent, regional nodal metastasis and perineural extension. Bloodvessels are clearly shown by MRI even without the use ofintravenous contrast. On the other hand, although MRI canalso demonstrate erosion

into the base of the skull by virtueof the change in signal of fatty bone marrow, CT scan isgenerally considered a better tool for defining bone erosion.The role of positron emission tomography scanning in NPC remains to be defined, although preliminary reports indicatethat it can be useful in detecting both local failures aftertreatment and distant metastases.

Prior to 1997, several different stage classifications wereused but that described by Ho [10] was found to be superior to the others in its ability to predict prognosis and treatment outcome[11]. However, Ho's classification was not ideal as aninternational system because it comprised five overall stages, there were only threeT-stages and it did not take into account CT scan evidence oftumor infiltration of the parapharyngeal region, a factor ofconsiderable prognostic significance.

The demonstration that tumor-derived DNA is detectable inthe plasma and serum of cancer patients raised the possibilitythat non-invasive detection and monitoring of NPC may befeasible. Using real-time quantitative PCR, cell-free EBVDNAwas found in the plasma of 96% of NPC patients and 7%of controls. Advanced-stage NPC patients had higher plasmaEBV-DNA levels than tumors with early-stage disease[12] Further studies have demonstrated that EBV-DNA may be avaluable tool for monitoring NPC patient response duringradiotherapy and chemotherapy, as well as early detectionof tumor recurrence.

MANAGEMENT

With advances in technology, the modern radiotherapy forNPC should be that of three-dimensional conformal or intensity-modulated with inverse radiotherapyplanning. Researchers at the University of Californian at SanFrancisco, Stanford University, University of Texas M.D. Anderson and Memorial Sloan–Kettering Cancer Centers have reported superior local control using such techniqueswhen compared with standard 2D methods. First, the successof 3DCRT or IMRT depends on better delineation of thetumor target by CT scan andMRI, images of which can be co-registered, such that 'geographicalmisses' are largely avoided. Secondly, there is cleardefinition of the vital organs in the vicinity ofthe NPC such that these organs are spared a heavy radiationdose, thus minimizing complications.In general the clinical target volume should includethe whole GTV and the structures in the vicinity of the tumor,which are at substantial risk of subclinical infiltration. Thesphenoid floor, the medial aspect of the greater wings of the sphenoid, the vomer, the posterior choanae, the pterygoid plates, the pterygopalatine fossa, the posterior wall of the maxillary sinus, the parapharyngeal spaces bilaterally[13] and the prevertebral muscles and fascia are all at risk of tumor infiltration andshould be included in the CTV.

ALTERED FRACTIONATION

In addition to improved radiotherapy techniques, use ofaltered fractionation and radiation dose escalation have beenreported to improve the local control. Although a Radiation Therapy Oncology Group trial has proved thesuperiority of both concomitant boost and hyperfractionation over the conventional daily fractionation for head and neck cancers in general, the benefit forNPC has not been addressed specifically. Subgroup analysisfor NPC was not possible in the RTOG trial due to the smallnumbers of NPC cases.

COMBINED MODALITY TREATMENT FORLOCO REGIONALLY ADVANCED DISEASE

Although the initial remission rate is substantial with radiotherapy alone even in locoregionally advanced, UICC stages III and IV disease, the subsequent rates of both local and distantfailures are high. Since NPC is highly chemosensitive, efforts have been made to incorporate chemotherapy into theprimary treatment of the disease.

CONCURRENT CHEMORADIOTHERAPY

Complete remission rates of locoregionally advanced diseaseto concurrent cisplatin radiotherapy in head and neck cancers, including NPC, were high and the early relapse-free survivalrates were promising.[14] Cisplatin acts both as a cytotoxicagent and as a radiation sensitizer. The optimal scheduling of cisplatin and radiation has not yet been established, but dailylow dose, weekly intermediate dose or 3-weekly high doseregimens have all been used.

TREATMENT FOR DISTANT METASTASES

The median survival for patients with distant metastases isaround 9 months. Several chemotherapeutic agents have beenused in the treatment of patients with locally recurrent andmetastatic NPC. Older agents including methotrexate, bleomycin, 5-FU, cisplatin and

carboplatin are the most activeagents, with response rates varying from 15% to 31%.Newer active agents include paclitaxel and gemcitabine withsingle agent response rates of 22 and 49%, respectively.

CONCLUSION

Nasopharyngeal carcinoma is a squamous cell carcinoma that usually develops around the ostium of the Eustachian tube in the lateral wall of the nasopharynx. In endemic regions, NPC presents as a complex diseasecaused by an interaction of the oncogenic gamma herpesvirus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process.Radiotherapyis the mainstay treatment for early disease and concurrent cisplatin/radiotherapy has been demonstrated to prolong survival in locoregionally advanced disease. Ongoing studies of targeting agents andimmunotherapeutic approaches may further improve treatment results.

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